Spontaneous bacterial peritonitis in adults: Treatment and prophylaxis

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INTRODUCTION — Spontaneous bacterial peritonitis (SBP) is defined as an ascitic fluid infection without an evident intra-abdominal surgically treatable source [1]. The presence of SBP, which almost always occurs in patients with cirrhosis and ascites, is suspected because of signs and symptoms such as fever, abdominal pain, or altered mental status (table 1). (See "Spontaneous bacterial peritonitis in adults: Clinical manifestations".)

The diagnosis is established by a positive ascitic fluid bacterial culture and an ascitic fluid absolute polymorphonuclear leukocyte count ≥250 cells/mm^3. Patients with SBP should be started on empiric, broad-spectrum antibiotics immediately after peritoneal fluid is obtained. When culture results are available, antibiotic coverage can be tailored to cover the specific organisms identified. (See "Spontaneous bacterial peritonitis in adults: Diagnosis".)

This topic will review the treatment and prophylaxis of SBP. The performance of paracentesis, the pathogenesis, clinical manifestations, and diagnosis of SBP, and the general evaluation of adults with ascites are discussed elsewhere. (See "Diagnostic and therapeutic abdominal paracentesis" and "Pathogenesis of spontaneous bacterial peritonitis" and "Spontaneous bacterial peritonitis in adults: Clinical manifestations" and "Spontaneous bacterial peritonitis variants" and "Spontaneous bacterial peritonitis in adults: Diagnosis" and "Evaluation of adults with ascites".)

In 2013, the American Association for the Study of Liver Diseases updated its guideline on the management of adult patients with ascites due to cirrhosis (table 2) [2,3]. The discussion that follows is consistent with that guideline.

TREATMENT — In patients with suspected spontaneous bacterial peritonitis (SBP), empiric therapy should be initiated as soon as possible to maximize the patient's chance of survival (algorithm 1 and table 2) [2,3]. However, antibiotics should not be given until ascitic fluid has been obtained for culture. Most cases of SBP are due to gut bacteria such as *Escherichia coli* and *Klebsiella*, though streptococcal and staphylococcal infections can also occur (table 3). As a result, broad-spectrum therapy is warranted until the results of susceptibility testing are available. We prefer cefotaxime 2 g intravenously every eight hours because it has been shown to produce excellent ascitic fluid levels. In addition to antibiotic therapy, patients with SBP who are taking a nonselective beta blocker should have the medication discontinued. (See "Spontaneous bacterial peritonitis in adults: Diagnosis", section on 'Obtaining ascitic fluid'.)

Discontinue nonselective beta blockers — Among patients with SBP, beta blocker use is associated with worse outcomes compared with those not receiving beta blockers. Because of this, we permanently

discontinue beta blockers once SBP has developed [4].

The effect of nonselective beta blocker use on outcomes was examined in a retrospective study of 607 patients with cirrhosis and ascites [4]. Once SBP developed, patients receiving a beta blocker had a 58 percent increase in mortality risk compared with patients who were not receiving a beta blocker (HR 1.58, 95% CI 1.10-2.27). In addition, rates of hepatorenal syndrome were higher (24 versus 11 percent) and length of hospital stay was longer (mean 29.6 versus 23.7 days).

Indications for antibiotic therapy — Empiric therapy for SBP should be started in a patient with ascites who has one or more of the following findings (table 1):

- Temperature greater than 37.8°C (100°F)
- Abdominal pain and/or tenderness
- A change in mental status
- Ascitic fluid polymorphonuclear leukocyte (PMN) count ≥250 cells/mm^3

Routine indications for treatment — In patients with fever, abdominal pain or tenderness, or altered mental status, treatment should be started as soon as ascitic fluid, blood, and urine have been obtained for culture and analysis. In patients without these findings, it is reasonable to wait until the results of the PMN count are available, with initiation of treatment if the ascitic fluid PMN count is ≥250 cells/mm^3 (algorithm 1). Collection and processing of the specimen should take no more than one to four hours from the time of the paracentesis. (See "Spontaneous bacterial peritonitis in adults: Diagnosis", section on 'Obtaining ascitic fluid'.)

The ascitic fluid PMN count is more rapidly available than the culture and appears to reliably identify patients who need empiric antibiotic coverage [1,5]. Delaying treatment until the ascitic fluid culture grows bacteria may result in death from overwhelming infection. (See "Spontaneous bacterial peritonitis in adults: Diagnosis", section on 'Ascitic fluid cell count'.)

Indications for treatment in patients with bacterascites — In some patients, infection is detected at the bacterascites stage (ie, bacteria are present in the ascitic fluid, but the PMN count is <250 cells/mm^3) [6]. Patients with bacterascites who progress to SBP commonly have signs or symptoms of infection (usually fever) at the time of the paracentesis [6,7]. Treatment should be started for patients with bacterascites who are symptomatic. For patients who are asymptomatic, a repeat paracentesis should be obtained after 48 hours (or if the patient develops symptoms) and treatment initiated if the PMN count has risen to ≥250 cells/mm^3. (See "Spontaneous bacterial peritonitis variants".)

Indications for treatment in patients with alcoholic hepatitis — Patients with alcoholic hepatitis regularly develop fever, peripheral leukocytosis, and abdominal pain that can mimic SBP. However, they also can develop SBP. Patients with a peripheral leukocytosis do not have a proportional increase in PMNs in ascitic fluid unless they also have SBP [8]; thus an elevated ascitic fluid PMN count must be presumed to represent SBP and empiric antibiotic therapy started. (See "Spontaneous bacterial peritonitis in adults: Diagnosis", section on 'Distinction from alcoholic hepatitis'.)

It is also reasonable to give empiric therapy to patients with alcoholic hepatitis who have a PMN count <250 cells/mm3, but who have fever and/or peripheral leukocytosis. Empiric antibiotic treatment can then be discontinued after 48 hours if ascitic fluid, blood, and urine cultures demonstrate no bacterial growth.

Choice of antibiotic — Most cases of SBP are due to gut bacteria such as *E. coli* and *Klebsiella*; however, streptococcal and, infrequently, staphylococcal infections can also occur (table 3). As a result, relatively broad-spectrum therapy is warranted in patients with suspected ascitic fluid infection. Clinical trials directly comparing different regimens are limited, and no antibiotic or combination of antibiotics has been proven to be superior to other regimens for the treatment of SBP. Our preference is to use intravenous cefotaxime 2 g every eight hours for most patients because it produces excellent blood and ascitic fluid levels throughout the dosing interval. Alternatives include other third-generation cephalosporins and fluoroquinolones.

The choice of antibiotics for treating SBP should take into account local resistance patterns and recent antibiotic use, and coverage should be rapidly narrowed when culture and sensitivity data are available. Antibiotic resistance is particularly a concern in patients who have received fluoroquinolones for SBP prophylaxis. Resistance to third-generation cephalosporins also appears to be an increasing concern, at least in some regions, particularly among patients with nosocomial infections or frequent contact with the healthcare system. (See 'Antibiotic resistance' below.)

Third-generation cephalosporins — Several antibiotic regimens have been shown to be effective for the treatment of SBP, but trials directly comparing different antibiotic regimens are lacking [9-15]. A third-generation cephalosporin is a reasonable choice for suspected SBP (algorithm 1) [1,5,10,16]. Our preference is to give cefotaxime 2 g intravenously every 8 hours. While ceftriaxone has been shown to prevent SBP in the setting of gastrointestinal hemorrhage in patients with cirrhosis [17], in our experience, cefotaxime is more effective than ceftriaxone for treating SBP. If ceftriaxone is used, patients should be given 2 g/day [18].

One randomized trial that examined cefotaxime included 73 patients with cirrhosis and severe infection (either SBP or bacteremia) [16]. The patients were assigned to cefotaxime or the combination of ampicillin and gentamicin. The following benefits were noted with cefotaxime:

- A higher rate of resolution of the infection (85 versus 56 percent), even though almost all of the organisms in both groups were sensitive to the antibiotics given
- No nephrotoxicity versus 5 percent with ampicillin-gentamicin
- No superinfection versus 14 percent with ampicillin-gentamicin

Dosing of cefotaxime 2 g intravenously every eight hours produces excellent ascitic fluid levels [19]. Lower doses or less frequent dosing can be used, especially in patients with impaired renal function. One study, for example, compared two different doses of cefotaxime in 143 patients with SBP: 2 g every 6 hours and 2 g every 12 hours [11]. The rate of infection resolution was the same in both groups (77 and 79 percent, respectively).

However, adjusting the dose of cefotaxime in patients with azotemia may not be necessary. We have used a dose of 2 g every eight hours in patients with a creatinine level >4 mg/dL (350 micromol/L) without toxicity [19]. Using cefotaxime in patients with azotemia may lead to high blood and ascitic fluid cefotaxime levels throughout the dosing interval, which in theory may result in improved bacterial killing. The main adverse drug reaction of cefotaxime is rash, which occurs in approximately 1 percent of patients.

Other antibiotics — Other antibiotics can be used for the treatment of SBP. Whenever possible, the antibiotics used should have been studied for the treatment of SBP. Levofloxacin can be used for patients with a penicillin allergy, although it does not penetrate into ascitic fluid to the same extent as cefotaxime. Fluoroquinolones should **not** be used in a patient who had been receiving a fluoroquinolone for SBP prophylaxis because the infecting organism may be resistant to fluoroquinolones. Organisms infecting

patients who have been on fluoroquinolone prophylaxis are usually (94 percent) susceptible to cefotaxime [20]. Nephrotoxic antibiotics should be avoided because the underperfused kidneys in cirrhosis tend to be exquisitely sensitive to injury [21]. (See "Manifestations of and risk factors for aminoglycoside nephrotoxicity".)

Certain oral agents may be as effective as parenteral therapy in the treatment of uncomplicated SBP. One trial, for example, included 123 patients with SBP (who were not vomiting or in shock) who were randomly assigned to ofloxacin 400 mg twice daily or parenteral cefotaxime [22]. The infection resolution rates were 84 and 85 percent, respectively. Another trial demonstrated comparable outcomes with a short course of intravenous ciprofloxacin (200 mg every 12 hours for two days) followed by oral ciprofloxacin therapy (500 mg every 12 hours for five days) compared with intravenous therapy alone [23]. In our experience, we have successfully used oral therapy in patients with asymptomatic SBP.

However, confirmatory trials are needed before oral treatment of this life-threatening infection can be routinely recommended.

Antibiotic resistance — A concern related to the choice of antibiotics is the emergence of resistant infections, especially in centers that use fluoroquinolones for SBP prophylaxis. Cefotaxime is appropriate treatment in patients who have been receiving SBP prophylaxis with a fluoroquinolone.

Resistance to fluoroquinolones was illustrated in a report from a center in Spain where norfloxacin prophylaxis is used routinely [24]. Multiresistant bacteria comprised 18 percent of total bacterial infections. These changes in flora and susceptibility were attributed to use of norfloxacin prophylaxis and invasive procedures (eg, intravascular lines and urinary catheters). Many liver units have avoided the use of urinary catheters for decades. This study provides some data to support the wisdom of this policy. (See 'Indications for antibiotic prophylaxis' below.)

Resistance to third-generation cephalosporins also appears to be an increasing concern, at least in some regions. A report of 246 episodes of SBP in Spain found that 22 percent of cases were caused by strains that were resistant to ceftriaxone (mainly extended-spectrum beta-lactamase-producing Gram-negative bacilli and Enterococci) [25]. The risk of resistance was related to patient characteristics and the clinical context. It was highest in nosocomially acquired cases (41 percent) and in patients with frequent contact with the healthcare system (22 percent), compared with only 7 percent among community-acquired cases. In settings where resistance to third-generation cephalosporins has been documented, levofloxacin can be used empirically as an alternative to cefotaxime, although there is much less clinical experience.

Duration of therapy — Trials have found that short-courses of treatment for SBP are effective. Many patients will respond to a treatment course of five days.

One randomized trial compared 5- and 10-day courses of cefotaxime in 90 patients with SBP [26]. The two groups had similar rates of bacteriologic cure (93 versus 91 percent), recurrent infection (11.6 versus 12.8 percent), and infection-related mortality (0 versus 4.3 percent). Another randomized trial demonstrated that treating until 48 hours after signs and symptoms of infection have disappeared is also effective [11].

We treat most patients for five days, including patients who are bacteremic (as they did in the 5- versus 10-day trial). Only patients who grow an unusual organism (eg, pseudomonas, Enterobacteriaceae), an organism resistant to standard antibiotic therapy, or an organism routinely associated with endocarditis (eg, *Staphylococcus aureus* or viridans group streptococci) are initially considered for longer treatment [26]. After

five days, we reassess the patient. Treatment is discontinued if there has been the usual dramatic improvement. However, if fever or pain persists, paracentesis is repeated, and the decision to continue or discontinue treatment is determined by the PMN response:

- If the PMN count is <250 cells/mm^3, treatment is stopped.
- If the PMN count is greater than the pretreatment value, a search for a surgical source of infection is undertaken. (See "Spontaneous bacterial peritonitis in adults: Diagnosis", section on 'Distinguishing spontaneous from secondary bacterial peritonitis'.)
- If the PMN count is elevated but less than the pretreatment value, antibiotics are continued for another 48 hours, and paracentesis is repeated.

Special treatment considerations

Albumin administration for patients with renal dysfunction — Renal failure develops in 30 to 40 percent of patients with SBP and is a major cause of death [27]. The risk may be decreased with an infusion of intravenous albumin (1.5 g per kg body weight within six hours of diagnosis and 1.0 g/kg body weight on day three) [28]. Albumin infusion should be given if the creatinine is >1 mg/dL (88 micromol/L), the blood urea nitrogen is >30 mg/dL (10.7 mmol/L), or the total bilirubin is >4 mg/dL (68 micromol/L) [29]. Once renal failure has developed, treatment with a combination of octreotide and midodrine may be helpful. (See "Hepatorenal syndrome".)

The development of renal failure is associated with activation of the renin-angiotensin system and a decrease in effective arterial volume. Thus, it has been hypothesized that plasma volume expansion could attenuate the hemodynamic changes in patients with SBP, thereby preserving renal function. A meta-analysis of four randomized trials (with a total of 288 patients) evaluated the impact of albumin infusion (in addition to antibiotics) on renal impairment and mortality in patients with SBP [30]. Albumin infusion was associated with a significant decrease in the incidence of renal impairment (8 versus 31 percent) and a significant reduction in mortality (16 versus 35 percent).

Secondary bacterial peritonitis and polymicrobial infections — Patients with suspected secondary bacterial peritonitis should receive broader coverage with cefotaxime and metronidazole. A similar regimen should be used with polymicrobial bacterascites [31]. (See "Spontaneous bacterial peritonitis variants".)

Culture-negative neutrocytic ascites — Patients with an ascitic fluid PMN count ≥250 cells/mm^3 who have negative ascitic fluid cultures have culture-negative neutrocytic ascites. Most patients with culture-negative neutrocytic ascites actually have SBP. Like other patients with a PMN count ≥250 cells/mm^3, patients with culture-negative neutrocytic ascites should receive empiric broad-spectrum antibiotics. However, because the cultures are negative, the antibiotic regimen cannot subsequently be tailored based on the results of sensitivity testing. (See "Spontaneous bacterial peritonitis variants".)

Repeat paracentesis — A follow-up ascitic fluid analysis to document resolution of the infection (ie, the culture is now sterile) and a marked decrease in PMN count is not needed in most patients treated for SBP. The majority of patients have a typical history including advanced cirrhosis, characteristic symptoms and ascitic fluid analysis (total protein concentration <1 g/dL [10g/L], glucose concentration >50 mg/dL [2.8 mmol/L], and lactate dehydrogenase less than the upper limit of normal for serum), infection with a single organism, and a dramatic clinical response. Repeat paracentesis is not necessary in such patients. (See "Spontaneous bacterial peritonitis in adults: Diagnosis", section on 'Interpretation of ascitic fluid test results'.)

However, repeat paracentesis should be performed if the setting, symptoms, ascitic fluid analysis, organism(s), or response to treatment are atypical. Lack of resolution of the infection raises the possibility of secondary peritonitis and should prompt further evaluation and, when appropriate, surgical intervention. (See 'Duration of therapy' above and "Spontaneous bacterial peritonitis in adults: Diagnosis", section on 'Distinguishing spontaneous from secondary bacterial peritonitis'.)

Prognosis — The infection-related mortality from SBP is low with appropriate treatment [1]. Several reports found no infection-related deaths if treatment was started prior to shock or frank renal failure [22,26]. In one systematic review, in-hospital mortality was best predicted by the presence of renal dysfunction (mortality rate 67 versus 11 percent in those with and without renal dysfunction respectively) and higher MELD scores [32].

In patients who have developed septic shock, mortality is high, but early initiation of appropriate antimicrobial therapy is associated with improved outcomes. In a retrospective study of 126 patients with cirrhosis and SBP-associated septic shock, the overall in-hospital mortality rate was 82 percent [33]. Patients who survived received antimicrobial therapy earlier than those who died (median delay 1.8 versus 9.5 hours). The adjusted odds ratio for mortality was 1.9 for every hour delay in administering antimicrobial therapy (95% CI 1.1-3.1). This study reinforces the recommendation to obtain ascetic fluid cultures immediately and then initiate empiric antimicrobial therapy in a patient with suspected SBP to maximize the patient's chance of survival, particular if the patient has developed sepsis. (See 'Treatment' above.)

Regardless of the short-term outcome related to the SBP, patients who have liver disease severe enough to develop SBP have a poor long-term prognosis. In-hospital, non-infection-related mortality may be as high as 20 to 40 percent [22,26], and one- and two-year mortality rates are approximately 70 and 80 percent, respectively [34,35]. Thus, liver transplantation should be seriously considered for survivors of SBP who are otherwise good transplantation candidates. (See "Liver transplantation in adults: Patient selection and pretransplantation evaluation".)

PROPHYLAXIS — Antibiotic prophylaxis for patients with risk factors for spontaneous bacterial peritonitis (SBP) (including ascitic fluid protein concentration <1 g/dL, variceal hemorrhage, or a prior episode of SBP) decreases the risk of bacterial infection and mortality. Prophylactic regimens include:

- History of SBP: Prolonged outpatient trimethoprim-sulfamethoxazole therapy (one double-strength tablet once daily) or fluoroquinolone therapy (eg, ciprofloxacin 500 mg/day or norfloxacin 400 mg/day [not available in the United States]).

- Inpatients with an ascitic protein concentration of less than 1 g/dL or <1.5 g/dL (10 or 1.5 g/L) who are hospitalized for a reason other than SBP or gastrointestinal bleeding: Treatment with trimethoprim-sulfamethoxazole (one double-strength tablet once daily) or fluoroquinolone therapy (ciprofloxacin 500 mg/day or norfloxacin 400 mg/day) while hospitalized. In the United States, the 1 g/dL threshold was validated whereas in the EU 1.5 g/dL was studied.

- Patients with cirrhosis and gastrointestinal bleeding: Initial treatment for patients with Child-Pugh class B or C cirrhosis is with intravenous ceftriaxone (1 g intravenously daily) followed by trimethoprim-sulfamethoxazole (one double-strength tablet twice daily), oral ciprofloxacin (500 mg orally every 12 hours), or norfloxacin (400 mg orally twice daily where available) once the patient is able to take medications by mouth. Patients with Child-Pugh class A cirrhosis can be managed with norfloxacin (400 mg orally twice daily; not available in the United States), trimethoprim-sulfamethoxazole (one double-strength tablet twice daily), or ciprofloxacin (500 mg orally every 12 hours or 400 mg IV every 12 hours).

The total number of days of antibiotic (parenteral and oral) is seven days.

In addition to decreasing infection rates and lowering mortality, prophylactic antibiotics may have the beneficial effects of increasing blood pressure and systemic vascular resistance [36]. These hemodynamic improvements, if sustained, may delay development of hepatorenal syndrome.

General measures — In addition to antibiotic prophylaxis, there are general measures that should be adopted to prevent SBP. These measures include:

- Diuretic therapy. Diuresis concentrates ascitic fluid, thereby raising ascitic fluid opsonic activity, which may help prevent SBP [37]. (See "Ascites in adults with cirrhosis: Initial therapy", section on 'Diuretic therapy'.)

- Early recognition and aggressive treatment of localized infections (eg, cystitis and cellulitis). This can help to prevent bacteremia and SBP.

- Restricting use of proton pump inhibitors. Proton pump inhibitor use has been associated with an increased risk of SBP in many (but not all) studies [38-40]. As a result, proton pump inhibitors should only be given to patients who have clear indications for their use [41].

Indications for antibiotic prophylaxis — Antibiotic prophylaxis to prevent SBP is recommended for patients at high risk of developing SBP and is associated with a decreased risk of bacterial infection and mortality [42-49]. However, the use of antibiotic prophylaxis can select for resistant bacteria that may subsequently cause spontaneous infection [44,47,50-53]. As a result, antibiotic prophylaxis should only be used in patients at high risk for SBP. (See "Pathogenesis of spontaneous bacterial peritonitis", section on 'Risk factors' and 'Antibiotic resistance' above.)

Guidelines suggest that antibiotic prophylaxis be given to the following patients [2,3]:

- Patients with cirrhosis and gastrointestinal bleeding. Antibiotic prophylaxis in this setting has been shown to decrease mortality in randomized trials [17].

- Patients who have had one or more episodes of SBP. In such patients, recurrence rates of SBP within one year have been reported to be close to 70 percent [34].

- Patients with cirrhosis and ascites if the ascitic fluid protein is <1.5 g/dL (15 g/L) along with either impaired renal function or liver failure. Impaired renal function is defined as a creatinine ≥1.2 mg/dL (106 micromol/L), a blood urea nitrogen level ≥25 mg/dL (8.9 mmol/L), or a serum sodium ≤130 mEq/L (130 mmol/L]). Liver failure is defined as a Child-Pugh score ≥9 and a bilirubin ≥3 mg/dL (51 micromol/L).

In addition, we give antibiotic prophylaxis to patients with cirrhosis who are hospitalized for other reasons and have an ascitic protein concentration of less than 1 g/dL (10 g/L).

There are no published randomized trials of antibiotic treatment for preventing infections in patients awaiting liver transplantation, so we base the decision to give antibiotic prophylaxis on whether the patient is at high risk for SBP.

In the early days of sclerotherapy, the use of long needles and contaminated endoscopic water sources led to bacteremia. Since the recognition of these problems and the use of shorter needles and sterile water, sclerotherapy-related infections have largely disappeared. Thus, parenteral antibiotics to prevent such

infections do not appear to be warranted. One study of 97 patients, for example, found a trend toward a lower incidence of bacteremia with imipenem-cilastin than with placebo (1.1 versus 5.6 percent) [54]. This difference was not statistically significant; furthermore, six of the seven episodes occurred after emergency sclerotherapy. Active bleeding appears to be the risk factor for infection in the current era—not sclerotherapy. In addition, variceal banding is now used much more often than sclerotherapy and is even less likely than sclerotherapy to lead to bacteremia [55].

Antibiotic regimen — The antibiotic regimen used for prophylaxis varies with the indication (table 2). Our general approach is as follows:

- For patients with a history of SBP, we use prolonged outpatient trimethoprim-sulfamethoxazole (one double-strength tablet daily). Alternatives include ciprofloxacin 500 mg/day or norfloxacin (400 mg/day; not available in the United States). We do not use weekly or five times per week dosing schedules.

- In patients with cirrhosis who are hospitalized for reasons other than SBP or gastrointestinal bleeding and have an ascitic protein concentration of less than 1 g/dL (10 g/L), we use oral trimethoprim-sulfamethoxazole (one double-strength tablet once daily) with discontinuation of the drug at the time of discharge [56]. Alternatives include ciprofloxacin (500 mg per day) or norfloxacin (400 mg/day) where available.

- In patients with advanced cirrhosis (Child-Pugh class B or C) and gastrointestinal bleeding, we use intravenous ceftriaxone 1 g intravenously daily and switch to oral trimethoprim-sulfamethoxazole (one double-strength tablet twice daily) once bleeding has been controlled and the patient is stable and eating [17]. Alternatives for oral therapy include ciprofloxacin (500 mg orally every 12 hours) or norfloxacin (400 mg twice daily) where available. Seven days of total antibiotic treatment are given. Patients with Child-Pugh class A cirrhosis can be managed with norfloxacin (400 mg orally twice daily), trimethoprim-sulfamethoxazole (one double-strength tablet twice daily), or ciprofloxacin (500 mg orally every 12 hours or 400 mg IV every 12 hours).

  The trial that validated ceftriaxone in this setting gave seven days of intravenous therapy [17]. However, patients hospitalized for variceal bleeding are regularly discharged prior to seven days. Switching to an oral regimen to complete the seven-day total antibiotic treatment allows patients to be discharged without having to arrange for outpatient administration of an intravenous antibiotic. (See "Approach to acute upper gastrointestinal bleeding in adults" and "General principles of the management of variceal hemorrhage".)

While trials have shown efficacy for both continuous (daily) and intermittent administration of antibiotic prophylaxis [48,57,58], intermittent dosing may select resistant flora more rapidly [59].

Efficacy — The efficacy of antibiotic prophylaxis to prevent SBP has been demonstrated in several studies and meta-analyses [42-49,60,61]. One meta-analysis included 13 randomized trials in which antibiotic prophylaxis was given to patients with cirrhosis and a variety of risk factors for infection (such as a low ascitic fluid protein concentration, gastrointestinal bleeding, or a history of SBP) [45]. The combined analysis showed an overall mortality benefit (RR 0.70, 95% CI 0.56-0.89) and a decrease in bacterial infections (RR 0.39, 95% CI 0.32-0.48). Similar conclusions were reached in subsequent meta-analyses [60,61].

The most compelling randomized trial compared norfloxacin with placebo in 68 patients with cirrhosis and ascitic fluid total protein <1.5 g/dL (15 g/L) who either had impaired renal function (serum creatinine ≥1.2

mg/dL [106 micromol/L], blood urea nitrogen ≥25 mg/dL [8.9 mmol/L], or serum sodium ≤130 mEq/L [130 mmol/L]) or liver failure (Child-Pugh score ≥9 points and serum bilirubin ≥3 mg/dL [51 micromol/L]) [49]. The patients treated with norfloxacin had fewer episodes of SBP (7 versus 61 percent), a lower rate of hepatorenal syndrome (28 versus 41 percent), and improved survival at 3 months (94 versus 62 percent) and at 12 months (60 versus 48 percent). It is unusual to demonstrate a survival advantage in treatment of a complication of advanced cirrhosis.

Cost-effectiveness — A cost-effectiveness analysis looking at the use of prophylactic antibiotics was performed by evaluating studies that used norfloxacin 400 mg once daily or trimethoprim-sulfamethoxazole one double-strength tablet five days per week for prophylaxis [62]. Compared with no prophylaxis, norfloxacin prophylaxis resulted in savings between $2216 and $8545 per patient per year, while trimethoprim-sulfamethoxazole prophylaxis resulted in savings between $2934 and $9251 per patient per year. The benefit of either regimen was minor in patients without a history of SBP. By comparison, higher savings were noted in patients with an ascitic fluid total protein concentration ≤1 g/dL or a previous episode of SBP. The analysis assumed that antibiotic prophylaxis remains effective in decreasing the frequency of SBP over an entire year; validation of this assumption requires extension of the follow-up period in clinical trials.

SUMMARY AND RECOMMENDATIONS

- Spontaneous bacterial peritonitis (SBP) should be suspected in a patient with ascites and any of the following (algorithm 1 and table 1 and table 2) (see 'Indications for antibiotic therapy' above):
  - Temperature greater than 37.8°C (100°F)
  - Abdominal pain and/or tenderness
  - A change in mental status
  - Ascitic fluid PMN count ≥250 cells/mm^3
- Most cases of SBP are due to gut bacteria such as *E. coli* and *Klebsiella*, though streptococcal and staphylococcal infections can also occur (table 3). (See 'Choice of antibiotic' above.)
- In patients receiving a nonselective beta blocker, we permanently discontinue the medication once SBP has developed because nonselective beta blocker use in this setting has been associated with decreased transplant-free survival, increased rates of hepatorenal syndrome, and more days of hospitalization compared with patients not receiving nonselective beta blockers. (See 'Discontinue nonselective beta blockers' above.)
- For patients with suspected SBP, while awaiting culture results, we suggest treatment with a third-generation cephalosporin (eg, cefotaxime) rather than narrower coverage (**Grade 2C**). Antibiotics used for the treatment of SBP should provide good coverage for the organisms commonly associated with SBP (eg, *E. coli*, *Klebsiella*) and should achieve good ascitic fluid levels. Cefotaxime (2 g intravenously every eight hours) or a similar third-generation cephalosporin provides appropriate microbial coverage and attains good ascitic fluid levels. A fluoroquinolone (eg, levofloxacin) is an alternative in patients who are allergic to penicillin. The selection of antibiotics for SBP should include consideration of local resistance patterns and recent antibiotic use (eg, a fluoroquinolone should not be used in a patient who has been receiving SBP prophylaxis with a fluoroquinolone). Antibiotic therapy should be tailored once the results of sensitivity testing are available. (See 'Choice of antibiotic' above.)
- We suggest treating most patients with SBP for five days rather than a longer course of therapy (**Grade**

2B). A longer course of therapy is appropriate for patients who grow an unusual organism (eg, pseudomonas, Enterobacteriaceae), an organism resistant to standard antibiotic therapy, or an organism routinely associated with endocarditis (eg, *S. aureus* or viridans group streptococci). In addition, a longer course of therapy is required for patients who fail to respond to therapy appropriately. (See 'Duration of therapy' above.)

After five days of treatment, we reassess the patient. Treatment is discontinued if there has been the usual dramatic improvement. However, if fever or pain persists, paracentesis is repeated, and the decision to continue or discontinue treatment is determined by the PMN response:

- If the PMN count is <250 cells/mm^3, treatment is stopped
- If the PMN count is greater than the pretreatment value, a search for a surgical source of infection is undertaken
- If the PMN count is elevated but less than the pretreatment value, antibiotics are continued for another 48 hours, and the paracentesis is repeated

- Renal failure develops in 30 to 40 percent of patients with SBP and is a major cause of death. The risk may be decreased with an infusion of intravenous albumin (1.5 g per kg body weight within six hours of diagnosis and 1.0 g/kg body weight on day 3). Albumin infusion should be given if the creatinine is >1 mg/dL (88 micromol/L), the blood urea nitrogen is >30 mg/dL (10.7 mmol/L), or the total bilirubin is >4 mg/dL (68 micromol/L). Once renal failure has developed, treatment with a combination of octreotide and midodrine may be helpful. (See 'Albumin administration for patients with renal dysfunction' above.)

- SBP responds well to appropriate antibiotic treatment. However, patients who have liver disease severe enough to develop SBP have a poor long-term prognosis. In-hospital, non-infection-related mortality may be as high as 20 to 40 percent, and one- and two-year mortality rates are approximately 70 and 80 percent, respectively. (See 'Prognosis' above.)

- We recommend antibiotic prophylaxis for patients at high risk for developing SBP, rather than waiting for SBP to develop to initiate antibiotic therapy (**Grade 1A**). In patients at high risk of developing SBP, antibiotic prophylaxis is associated with a decreased risk of bacterial infection and mortality. We also suggest that antibiotic prophylaxis be given continuously (daily) rather than intermittently (**Grade 2C**). Doing so may decrease the risk of bacterial antibiotic resistance. (See 'Indications for antibiotic prophylaxis' above and 'Antibiotic regimen' above and 'Efficacy' above.)

  Patients at high risk for SBP include (see "Pathogenesis of spontaneous bacterial peritonitis", section on 'Risk factors'):

  - Patients with cirrhosis and gastrointestinal bleeding.

  - Patients who have had one or more episodes of SBP (among whom recurrence of SBP within one year has been reported to be close to 70 percent).

  - Patients with cirrhosis and ascites if the ascitic fluid protein is <1.5 g/dL (15 g/L) along with either impaired renal function or liver failure. Impaired renal function is defined as a creatinine ≥1.2 mg/dL (106 micromol/L), a blood urea nitrogen level ≥25 mg/dL (8.9 mmol/L), or a serum sodium ≤130 mEq/L (130 mmol/L]). Liver failure is defined as a Child-Pugh score ≥9 and a bilirubin ≥3 mg/dL (51 micromol/L).

- Patients with cirrhosis who are hospitalized for other reasons and have an ascitic protein concentration of less than 1 g/dL (10 g/L).

- For patients who require prophylaxis, we use antibiotic regimens that have been specifically studied for SBP prophylaxis whenever possible. We use the following regimens (see 'Antibiotic regimen' above):

  - For patients with a history of SBP, we use prolonged outpatient trimethoprim-sulfamethoxazole (one double-strength tablet daily). Alternatives include ciprofloxacin 500 mg/day or norfloxacin (400 mg/day; not available in the United States). We do not use weekly or five times per week dosing schedules.

  - In patients with cirrhosis who are hospitalized for reasons other than SBP or gastrointestinal bleeding and have an ascitic protein concentration of less than 1 g/dL (10 g/L), we use oral trimethoprim-sulfamethoxazole (one double-strength tablet once daily) with discontinuation of the drug at the time of discharge. Alternatives include ciprofloxacin (500 mg per day) or norfloxacin (400 mg/day) where available.

  - In patients with advanced cirrhosis (Child-Pugh class B or C) and gastrointestinal bleeding, we use intravenous ceftriaxone 1 g intravenously daily and switch to oral trimethoprim-sulfamethoxazole (one double-strength tablet twice daily) once bleeding has been controlled and the patient is stable and eating. Alternatives for oral therapy include ciprofloxacin (500 mg orally every 12 hours) or norfloxacin (400 mg twice daily) where available. Patients with Child-Pugh class A cirrhosis can be managed with norfloxacin (400 mg orally twice daily), trimethoprim-sulfamethoxazole (one double-strength tablet twice daily), or ciprofloxacin (500 mg orally every 12 hours or 400 mg IV every 12 hours). Seven days of total antibiotic treatment are given.

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Topic 1248 Version 31.0

GRAPHICS

Signs and symptoms at the time of diagnosis in 489 patients with spontaneous bacterial peritonitis

Clinical feature	Percent with sign or symptom
Fever	69
Abdominal pain	59
Altered mental status	54
Abdominal tenderness	49
Diarrhea	32
Paralytic ileus	30
Hypotension	21
Hypothermia	17

Data from McHutchison JG, Runyon BA. Spontaneous bacterial peritonitis. In: Gastrointestinal and Hepatic Infections, Surawicz CM, Owen RL (Eds), WB Saunders Company, Philadelphia 1994. p.455.

Graphic 71038 Version 2.0

American Association for the Study of Liver Diseases (AASLD) recommendations for the management of adult patients with ascites due to cirrhosis

Evaluation and diagnosis
Abdominal paracentesis should be performed and ascitic fluid should be obtained from inpatients and outpatients with clinically apparent new-onset ascites.
Because bleeding is sufficiently uncommon, the routine prophylactic use of fresh frozen plasma or platelets before paracentesis is not recommended.
Differential diagnosis
The initial laboratory investigation of ascitic fluid should include an ascitic fluid cell count and differential, ascitic fluid total protein, and serum-ascites albumin gradient (SAAG).
If ascitic fluid infection is suspected, ascitic fluid should be cultured at the bedside in blood culture bottles prior to initiation of antibiotics.
Other studies of ascitic fluid can be ordered based on pretest probability of disease.
Testing serum for CA125 is not helpful in the differential diagnosis of ascites. Its use is not recommended in patients with ascites of any type.
Treatment of ascites
Patients with ascites who are thought to have an alcohol component to their liver injury should abstain from alcohol consumption.
Baclofen can be given to reduce alcohol craving and alcohol consumption in patients with ascites in the setting of alcoholic liver disease.
Firstline treatment of patients with cirrhosis and ascites consists of sodium restriction (88 mmol/day [2000 mg/day]) and diuretics (oral spironolactone with or without oral furosemide).
Fluid restriction is not necessary unless serum sodium is less than 125 mmol/L.
An initial therapeutic abdominal paracentesis should be performed in patients with tense ascites. Sodium restriction and oral diuretics should then be initiated.
Diuretic-sensitive patients should preferably be treated with sodium restriction and oral diuretics rather than with serial paracenteses.
Use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers may be harmful and must be carefully considered in each patient. Patients on one of these agents require blood pressure and renal function monitoring.
The use of nonsteroidal anti-inflammatory drugs should be avoided in patients with cirrhosis and ascites, except in special circumstances.
Liver transplantation should be considered in patients with cirrhosis and ascites.
Refractory ascites
Patients with refractory ascites may have increased mortality with beta blockers. The risks versus benefits of beta blockers must be carefully weighed in these patients.
Angiotensin converting enzyme inhibitors and angiotensin receptor blockers should be avoided in patients with refractory ascites.
Oral midodrine has been shown to improve clinical outcomes and survival in patients with refractory ascites, and its use should be considered.
Serial therapeutic paracenteses are a treatment option for patients with refractory ascites.
Postparacentesis albumin infusion may not be necessary for a single paracentesis of less than 4 to 5 L.

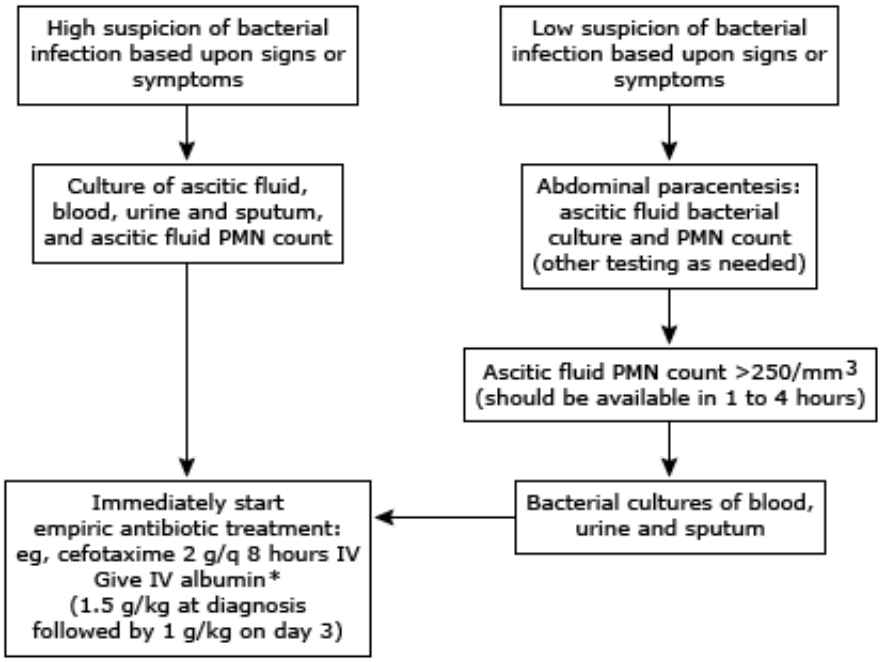
For large-volume paracenteses, an albumin infusion of 6 to 8 g/L of fluid removed can be considered.
Referral for liver transplantation should be expedited in patients with refractory ascites.
Transjugular intrahepatic portasystemic stent-shunt (TIPS) may be considered in appropriately selected patients who meet criteria similar to those of published randomized trials.
Peritoneovenous shunt, performed by a surgeon experienced with this technique, should be considered for patients with refractory ascites who are not candidates for paracenteses, transplant, or TIPS.
Hepatorenal syndrome
Urinary biomarkers such as neutrophil gelatinase associated lipocalin may assist in the differential diagnosis of azotemia in patients with cirrhosis.
Albumin infusion plus administration of vasoactive drugs such as octreotide and midodrine should be considered in the treatment of type I hepatorenal syndrome.
Albumin infusion plus administration of norepinephrine should be considered in the treatment of type I hepatorenal syndrome when the patient is in the intensive care unit.
Patients with cirrhosis, ascites, and type I or II hepatorenal syndrome should have an expedited referral for liver transplantation.
Spontaneous bacterial peritonitis (SBP)
Patients with ascites admitted to the hospital should undergo abdominal paracentesis. Paracentesis should be repeated in patients (whether in the hospital or not) who develop signs or symptoms or laboratory abnormalities suggestive of infection (eg, abdominal pain or tenderness, fever, encephalopathy, renal failure, acidosis, or peripheral leukocytosis).
Patients with ascitic fluid PMN counts ≥250 cells/mm^3 (0.25 X 10^9/L) should receive empiric antibiotic therapy, eg, an intravenous third-generation cephalosporin, preferably cefotaxime 2 g every 8 hours.
Oral ofloxacin (400 mg twice per day) can be considered a substitute for intravenous cefotaxime in inpatients without prior exposure to quinolones, vomiting, shock, grade II (or higher) hepatic encephalopathy, or serum creatinine >3 mg/dL.
Patients with ascitic fluid polymorphonuclear leukocyte (PMN) counts <250 cells/mm^3 (0.25 X 10^9/L) and signs or symptoms of infection (temperature >100°F or abdominal pain or tenderness) should also receive empiric antibiotic therapy, eg, intravenous cefotaxime 2 g every 8 hours, while awaiting results of cultures.
When the ascitic fluid of a patient with cirrhosis is found to have a PMN count ≥250 cells/mm^3 (0.25 X 10^9/L) and there is high suspicion of secondary peritonitis, it should also be tested for total protein, LDH, glucose, Gram stain, carcinoembryonic antigen, and alkaline phosphatase to assist with the distinction of SBP from secondary peritonitis. Computed tomographic scanning should also be performed.
Patients with ascitic fluid PMN counts ≥250 cells/mm^3 (0.25 X 10^9/L) in a nosocomial setting and/or recent beta-lactam antibiotic exposure and/or culture of an atypical organism(s) or an atypical clinical response to treatment should undergo a follow-up paracentesis after 48-hours of treatment to assess the response in PMN count and culture.
Patients with ascitic fluid PMN counts ≥250 cells/mm^3 (0.25 X 10^9/L) and clinical suspicion of SBP, who also have a serum creatinine >1 mg/dL, blood urea nitrogen >30 mg/dL, or total bilirubin >4 mg/dL should receive 1.5 g albumin/kg body weight within 6 hours of detection and 1.0 g/kg on day three.
Prevention of spontaneous bacterial peritonitis
Intravenous ceftriaxone for seven days or twice-daily norfloxacin for seven days should be given to prevent bacterial infections in patients with cirrhosis and gastrointestinal hemorrhage.
Patients who have survived an episode of SBP should receive long-term prophylaxis with daily norfloxacin (or trimethoprim/sulfamethoxazole) because this is the most data-supported indication for long-term outpatient prophylaxis.
In patients with cirrhosis and ascites but no gastrointestinal bleeding, long-term use of norfloxacin (or

trimethoprim/sulfamethasoxazole) can be justified if the ascitic fluid protein <1.5 g/dL and at least one of the following is present: serum creatinine ≥1.2 mg/dL, blood urea nitrogen ≥25 mg/dL, serum sodium ≤130 mEq/L, or Child-Pugh ≥9 points with bilirubin ≥3 mg/dL.
Intermittent dosing of antibiotics to prevent bacterial infections may be inferior to daily dosing (due to the development of bacterial resistance) and thus daily dosing should preferentially be used.
Hepatic hydrothorax
Chest tube insertion is contraindicated in patients with hepatic hydrothorax.
First-line therapy of hepatic hydrothorax consists of dietary sodium restriction and diuretics.
TIPS can be considered as second-line treatment for hepatic hydrothorax once it becomes refractory to sodium restriction and diuretics.
Additional considerations
The risks versus benefits of hernia repair must be weighed carefully in patients with cirrhosis and ascites. Elective repair can be performed during or after liver transplantation.
Elective repair of a hernia in a patient with cirrhosis is best performed after ascites has been controlled by medical treatment, the patient's overall condition has been optimized, and a multidisciplinary approach with consideration of perioperative TIPS is utilized.
Emergent repair of a strangulated or perforated umbilical hernia is best performed by a surgeon who is experienced in the care of patients with cirrhosis.
Cellulitis can explain pain and fever in patients with cirrhosis and ascites and should be treated with diuretics and antibiotics.
Percutaneous endoscopic gastrostomy tube placement should be avoided in patients with cirrhosis and ascites.

Data from: Runyon BA. Management of adult patients with ascites due to cirrhosis: Update 2012. http://www.aasld.org/sites/default/files/guideline_documents/adultascitesenhanced.pdf (Accessed on April 26, 2013).

Graphic 70375 Version 5.0

Approach to the management of suspected spontaneous bacterial peritonitis



PMN: polymorphonuclear leukocyte; IV: intravenous.
* Albumin infusion should be given if the creatinine is >1 mg/dL (88 micromol/L), the blood urea nitrogen is >30 mg/dL (10.7 mmol/L), or the total bilirubin is >4 mg/dL (68 micromol/L).

Graphic 59554 Version 2.0

Bacteria isolated from ascitic fluid in 519 patients with spontaneous bacterial peritonitis

Organism	Percent of isolates
Escherichia coli	43
Klebsiella pneumoniae	11
Streptococcus pneumoniae	9
Other streptococcal species	19
Enterobacteriaceae	4
Staphylococcus	3
Pseudomonas	1
Miscellaneous*	10

*In some regions of the world, such as Korea, Aeromonas hydrophila infection is an important cause of SBP, particularly in warm weather months. Affected patients commonly also have diarrhea. [Choi JP, et al. Clin Infect Dis 2008; 47:67.]

Data from McHutchison JG, Runyon BA. Spontaneous bacterial peritonitis. In: Gastrointestinal and Hepatic Infections, Surawicz CM, Owen RL (Eds), WB Saunders, Philadelphia 1995. p.455.

Graphic 80188 Version 3.0

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